Clinical Proceedings

of the

CHILDREN'S HOSPITAL

WASHINGTON, D. C.

Contents

Vol. III MARCH 1947 No. 4

Entered as second class matter November 21, 1946 at the post office at Washington, D. C., under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 538, Act of February 28, 1925, authorized January 17, 1947.

Published monthly by the Children's Hospital, 13th and W Sts., Washington, D. C.

Subscription rate is $1.00 per year.

*SPECIAL REPORT**

ACUTE GLOMERULONEPHRITIS

A Review of 90 Cases

Frederic Gerard Burke, M.D. and Sidney Ross, Lt. (j.g.) (MC) U.S.N.R.

This report is an analysis of a series of 90 consecutive cases of acute glomerulonephritis which have been managed at the Children's Hospital during a three year period (1943–45). There were 34 white and 56 colored; 46 were males, and 44 were females. It is to be noted that there was only a slight preponderance in the number of male cases with acute glomerulonephritis in our series in contrast to the several large series reported by other authors[1] who found a rather noticeable predilection for males. Lyttle[2] in his report on 125 cases of acute nephritis in children observed nearly a 2:1 ratio in males. The average age of the 90 cases was 5.7 years; the majority were between the ages of 2 and 10 years and the youngest patient was 4 months (Chart 1).

ONSET OF CLINICAL MANIFESTATIONS

The onset of symptoms began either simultaneously with or shortly after an acute febrile disease in 86 per cent of the cases in this series. A history of a preceeding illness was not obtained in seven cases. A hiatus of 7 to 14 days after the subsidence of the symptoms of the primary infection was most common, but several patients were admitted with an accompanying infection of the respiratory tract or skin.

The most common predisposing infections were those of the upper respiratory tract including nasopharyngitis, tonsillitis and otitis media; a history of such an infection was obtained in 65.3 per cent. It has been reported[3] that a "deep" hemolytic Streptococcal infection precedes the onset of acute nephritis in about two thirds of the cases. However, in our series the severity of the preceding upper respiratory infection appeared to be of no particular significance since many of the precipitating infections were quite mild (Chart 2).

Skin diseases such as secondarily infected burns, impetigo and infected eczema form the next largest group of preceding infections (10.2 per cent). Futcher[4] has recently reviewed the role of skin infections in the etiology of acute glomerulonephritis and reported the incidence to vary from 0 to 28 per cent. Scarlet fever was the cause in three cases (3.3 per cent) but

* Summary of an article in the February issue of the Journal of Pediatrics. Reprinted with the permission of the Editor, Dr. Borden Veeder.

may be a more common predisposing infection than this figure would indicate; however, the contagion service of the Children's Hospital is rather small and most cases of scarlet fever are referred elsewhere. The remaining group had a history of some other infection including pneumonia, sinusitis,

CHART 1

AGE, COLOR AND SEX DISTRIBUTION IN 90 CASES OF ACUTE GLOMERULONEPHRITIS

	NO. OF CASES	PER CENT
1. Age		
0–1 yrs.	2	2.3
1–5 yrs.	36	40.0
5–12 yrs.	52	57.7
2. Color		
Negro	56	62.3
White	34	37.7
3. Sex		
Male	46	51.1
Female	44	48.9

CHART 2

PRECEDING INFECTIONS IN THE PRESENT SERIES OF 90 CASES OF ACUTE GLOMERULONEPHRITIS

TYPE OF INFECTION	NO. OF CASES	PER CENT
URI (pharyngotonsillitis, otitis media)	59	65.3
Skin lesions	9	10.2
Scarlet fever	3	3.3
Mumps	2	2.2
G I infections	2	2.2
Pneumonia	2	2.2
Adenitis	2	2.2
Sinusitis	2	2.2
G U infections	1	1.1
Syphilis	1	1.1
Unknown	7	8.0
Total	90	

mumps, cervical adenitis and others. In three cases, two of which fall outside of the time limit of this series, acute nephritis occurred with congenital syphilis. All three were under one year of age. It is problematical whether this association between congenital syphilis and acute nephritis represents a primary invasion of the kidney by the treponema pallidum or a secondary involvement of the kidney resulting from the upper respiratory infection frequently found to coexist with congenital syphilis.

In this regard, it is well to point out that congenital syphilis is the most common precursor of acute glomerulonephritis in patients under one year of age.[5]

Etiologic studies were not carried out in every case but beta hemolytic Streptococci were found most frequently on throat culture while Staphylococcus aureus was usually the organism cultured from coexisting skin infections.

PRESENTING SYMPTOMS

The presenting symptoms in this series constitutes an interesting analysis (Chart 3). Edema, as might be expected, was the outstanding symptom in 59.5 per cent of the cases. Next in frequency was gross hematuria which was the chief complaint in 25.5 per cent. Abdominal pain was present at

CHART 3

PRESENTING MANIFESTATIONS OF ACUTE GLOMERULONEPHRITIS IN CURRENT SERIES

MANIFESTATION	NO. OF CASES	PER CENT
Edema	54	59.5
Hematuria	23	25.5
Abdominal pain	6	7.0
Vomiting	2	2.2
Convulsions	2	2.2
Dyspnea	2	2.2
Dysuria	1	1.1
Total	90	

one time or another in one-third of the cases and in six, comprising seven per cent of the total number, was the presenting and chief complaint. In several cases the diagnosis of appendicitis was entertained upon admission, especially in those cases accompanied by nausea and vomiting; however, this pain was usually peri-umbilical or located in the right upper quadrant. Its origin was probably a distended, congested liver with stretching of Glisson's capsule due to heart failure in several patients. Dyspnea was occasionally noted especially in the group with demonstrable myocardial damage, and was the main complaint upon admission in two cases. Convulsions and coma were the presenting symptoms in two other patients and in one case nephritis was diagnosed by routine urinalysis after the child was admitted with a diagnosis of pneumonia.

MAJOR MANIFESTATIONS (CHART 4)

1. *Hematuria and Albuminuria.* These two findings constituted the diagnostic criteria of acute glomerulonephritis and were present in every

case. It is interesting to note that in at least three cases in this series, the impression of acute glomerulonephritis was entertained in view of the presence of several other manifestations of the disease, but the diagnosis was not definitely established until a second or third urine revealed hematuria after 24 to 48 hours, the initial urinalysis showing no abnormalities of the urinary sediment. Red blood cells varied in amount. Gross hematuria was present in approximately one-fourth of the cases and microscopic hematuria was found in the remainder. The amount of albumin varied from 50 to 2000 mgm. per cent but the usual range was between 100 and

CHART 4

FREQUENCY OF OCCURRENCE OF MAJOR MANIFESTATIONS IN 90 CASES OF ACUTE GLOMERULONEPHRITIS

MANIFESTATION	NO. OF CASES	PER CENT
Hematuria	90	100
Albuminuria	90	100
Edema	74	84.4
Hypertension	73	81.1
Congestive heart failure		57
Abdominal pain	35	33.3
Cerebral symptoms	28	31.1

CHART 5

OUTCOME IN 90 CASES OF ACUTE GLOMERULONEPHRITIS

OUTCOME	NO. OF CASES	PER CENT
Recovered	84	93.4
Died	3	3.3
Chronic	3	3.3
Total	90	

500 mgm. per cent on initial urinalysis; the albuminuria disappeared in the majority of instances within four weeks after the onset of the initial symptoms. Casts were frequently noted. Daily examination of the urine was employed during the hospital course and reliance was placed on the correlation between the gradual disappearance of the urinary findings and the subsidence of the illness.

2. *Edema.* Edema is the most common symptom of acute nephritis and was present in 84.4 per cent of the ninety cases in this series. It was not clinically perceptible in 16 per cent, was minimal in 37 per cent, moderate in 28 per cent and severe in 19 per cent. The cases of nephritis without edema usually posed the diagnostic problems in this group. Classically,

the edema usually developed in the face, particularly in the low tension tissues in the infraorbital region. It often was confined to this area but not infrequently continued to develop and appeared in the lower extremities and subsequently in all the subcutaneous tissues, serous spaces and viscera. The patient who develops edema of the face only to have it disappear and then reappear later on must be regarded as a potential candidate for classification as a case of subacute or chronic nephritis. It is noteworthy that in all the patients in this series who went on to recovery, the edema was progressive or came to a standstill and was not intermittent.

3. *Hypertension.* Significant elevation of the blood pressure was present in 81.1 per cent of the cases in this series. Arbitrarily, in agreement with other observers, 120 mm. systolic pressure was selected as the dividing line for the presence or absence of *significant hypertension* although it is appreciated that in young children, particularly those under the age of five years, a systolic pressure of 120 mm. may well constitute hypertension.

At least one systolic blood pressure reading above 140 mm. was observed in 44 per cent of the cases and pressures ranging between 120 and 140 mm. in 30 per cent. The blood pressure was usually elevated at the time of admission although in eleven cases it never did rise while under observation. One notable case among this group without significant hypertension died shortly after admission of acute nephritic congestive heart failure. In nearly all cases showing marked cardiac manifestations a significant elevation of the blood pressure was noted. Marked hypertension as a sine qua non in the presence of congestive heart failure associated with acute glomerulonephritis has been the subject of some discussion. It was present in all of the 14 cases of nephritic heart failure in children reported by Rubin and Rapoport[6]. On the other hand, Levy[7] and Lyttle[2] have reported cases in which this association was not observed. In the present series, three cases of heart failure were not accompanied by significant blood pressure elevation.

Occasionally, the blood pressure was noted to rise considerably after admission, particularly in those cases who were admitted to the hospital at the very onset of the illness. However, in the majority of instances the highest readings observed were at the time of admission and under treatment fell over a period of one to two weeks to normalcy. The systolic pressure was found to be a reliable guide to the degree of hypertension and in most instances the diastolic pressure followed the systolic; however, in a few cases the systolic pressure remained within relatively normal range while an elevated diastolic pressure was observed. It is probably fair to assume that if all patients with acute glomerulonephritis could be adequately followed from the very first day of their illness during the entire course, a larger percentage might well show a significant hypertension.

4. *Cerebral.* Cerebral symptoms in this disease are probably caused by

vasospasm with secondary cerebral ischemia. Vasospasm is probably also the cause of the hypertension. The evidence would indicate that cerebral edema plays an unimportant role in the etiologic background of the manifestations of encephalopathy associated with acute glomerulonephritis.

Cerebral symptoms in this series were present in 31.1 per cent of the cases. All of these patients had severe headaches, convulsions or were in coma. These three symptoms were the diagnostic criteria employed and an associated moderate or severe hypertension was usually present. In general these symptoms indicate a severe type of acute glomerulonephritis. Some of the other patients manifested cerebral symptoms of a milder degree such as slight headaches, restlessness and dimness of vision.

5. *Cardiac Manifestations.* It has long been known that cardiac failure may complicate the early stages of acute glomerulonephritis. In 1879, Goodhart[8] called attention to this association and since then many reports have appeared on the subject in the literature. Of particular note is Whitehill et al's. carefully studied series of 138 young adults with acute nephritis, 98, or 71 per cent of whom showed clinical evidence of cardiac insufficiency. Forty per cent of 80 cases reported by Marcolongo[10] and 33 per cent of the 24 cases reported by Master et al.[11] similarly exhibited cardiac failure. Lyttle[2] states that half of the 125 children with acute nephritis studied at Babies' Hospital in New York, demonstrated cardiac failure, while 14 of the 55 cases of acute glomerulonephritis in children observed by Rubin and Rapoport[6] had congestive heartfailure associated with the disease.

Acute glomerulonephritis has been the most common cause of congestive heart failure at Children's Hospital during the period covered by this series and was present in 35, or 57 per cent of the 62 cases who were examined for evidence of this complication. The criteria used to diagnose heart failure were:

1. Cardiac enlargement with congestion of the lung parenchyma as revealed by x-ray.
2. Elevated venous pressure (using 160 mm. of normal saline as the maximal normal level) with a significant rise upon moderate pressure over the right upper quadrant.
3. Engorgement with definite enlargement of the liver.
4. Miscellaneous evidence including E.K.G. changes, pulsating cervical veins, pulmonary edema, dyspnea and direct evidence of autopsy.

Some patients had definite evidence of cardiac dilatation by X-ray which returned to normal size while under observation but confirmatory evidence of an elevated venous pressure and palpable liver were lacking and were not considered cases of congestive failure. However, if transient dilatation

may be interpreted as evidence of partial impairment of cardiac function and these cases are grouped with those exhibiting frank congestive failure, then a total of 72.6 per cent of the 62 patients who were examined for evidence of this manifestation had demonstrable myocardial damage with insufficiency.

The signs of congestive heart failure were present usually in the first week after the appearance of the initial symptoms of acute glomerulonephritis. Most commonly these signs were detected upon admission; however, in several cases it was possible to demonstrate by serial roentgenograms a delay of two to three days before significant enlargement occurred.

A transient diastolic murmur at the base was observed in one case with very severe decompensation and was interpreted as evidence of functional aortic regurgitation; this murmur disappeared when compensation occurred. Functional apical systolic murmurs were frequently noted but appeared to have no particular significance. Gallop rhythm was observed in five patients and is always to be regarded as a grave prognostic sign. It was present in two of the three patients who died.

The mechanism of heart failure associated with acute glomerulonephritis is not exactly known, but it is probable that there are several factors concerned with its production. The two most important of these appear to be (1) hypertension due to vascular spasm and (2) toxic changes in the myocardium probably vascular in origin but independent of hypertension. Elevation of the blood pressure may represent a trigger mechanism which tips over a damaged heart into congestive failure. While the vast majority of patients showing congestive heart failure had an associated elevation of blood pressure (95 per cent), it is worth while noting that three cases failed to demonstrate any significant elevation. One of these three died of congestive heart failure with a blood pressure of 110 mm. over 55 mm. Although the absence of hypertension in the presence of congestive heart failure associated with acute glomerulonephritis is relatively infrequent, the finding of even a few cases would suggest the importance of the role of underlying myocardial damage. The nature of this factor is not clearly understood. The theory that the disease represents a toxic generalized capillaritis of the entire vascular system including the myocardium with associated temporary damage is still accepted by most observers at the present time. Longcope et al.[12] have pointed out the intimate relationship existing between infections due to hemolytic Streptococci and the subsequent onset of acute nephritis. The association of cardiac damage with Streptococcal infections is well known. Brody and Smith[13] found heart lesions of varying degrees of severity in more than 90 per cent of the cases of scarlet fever and related Streptococcal infections which came to

autopsy. While the common myocardial lesions described in scarlet fever appear to be of an inflammatory nature, changes noted in the cardiac muscle of patients who died of acute hemorrhagic nephritis appear to be of a degenerative character. It has been suggested by Rubin and Rapoport[6] that if the renal lesion in acute hemorrhagic nephritis is anaphylactoid, it is possible that the cardiac involvement may be of a similar etiology.

Electrocardiographic evidence supports the theory of actual myocardial damage. Electrocardiograms were taken at random intervals during the course of 30 of the patients in the present series and abnormal records were found in 13 (43 per cent). The most common abnormal changes found were the flattening or inversion of the T waves, especially T1 and T2. Follow-up studies revealed that the myocardial damage was only temporary; all of the records were normal within 2 to 4 weeks after the onset of the nephritis in those patients who had shown abnormal readings initially. It is a fair presumption that if serial electrocardiograms had been taken in all cases, a larger percentage of abnormalities would have been recorded. Ash et al.[14] found significant variations in 72 per cent of 50 children with acute nephritis employing the serial method.

MINOR MANIFESTATIONS

Anemia of varying degrees of severity was a rather frequent finding in this series and was marked (Hgb. 8 gm. or less) in 20 per cent and moderate (Hgb. between 9 and 10 gm.) in 52 per cent of the cases.

Anuria was not observed in any instance but oliguria was noted not infrequently in the first few days of illness. The non-protein nitrogen blood level was above 35 mgm. per cent in 65 per cent of the cases and was normal in the remaining 35 per cent.

Fever was not characteristic of acute glomerulonephritis and was absent upon admission in 60 per cent of the cases. When an elevation of the temperature was present, usually an associated extra-nephritic infection could be simultaneously demonstrated.

A rapid sedimentation rate was a rather constant feature of nephritis during the acute phase of the disease.

PROGNOSIS AND RESULTS

Eighty-four or 93.4 per cent of the patients in this series recovered while three (3.3 per cent) died during the acute attack. Three (3.3 per cent) developed chronic glomerulonephritis and one of these patients died several months later of pneumonia. All of the cases that recovered have remained well in a follow-up period varying from a few months to two years. In no case was there any residual cardiac damage demonstrable.

A recrudescence of the symptoms of acute glomerulonephritis, partic-

ularly hematuria and albuminuria may be precipitated by secondary acute upper respiratory infections or by one of the common contagious diseases acquired during the convalescent period. This, however, cannot be considered as a second attack of acute glomerulonephritis but rather an exacerbation of the original disease process. Nor does such an exacerbation necessarily predicate a bad prognosis. In two such instances a recurrence of albuminuria and hematuria was noted during the convalescent period after apparent recovery; in one of these patients, mumps was the complicating secondary infection and in the other, chickenpox. However, in both cases the urinary abnormalities subsided within three to four weeks and the patients went on to complete recovery.

The low incidence of chronic nephritis as a complication in this series is in accord with several other reports. The three cases of chronic glomerulonephritis developed after an apparently acute onset and very early in the course of their disease showed large amounts of albumin in the urine out of proportion to the number of red cells. This disproportion of albuminuria to hematuria was regarded as a significant prognostic indication of the development of chronic nephritis. The high incidence of subacute and chronic glomerulonephritis following acute glomerulonephritis reported in adults[9] has not been observed in this series of children.

In one of the cases who went on to chronic glomerulonephritis the onset and presenting symptoms were indistinguishable from those who completely recovered. However, early in the course of the disease this patient showed a gradual disappearance of red cells from the urinary sediment associated with increasing amounts of albuminuria. At the end of a one year follow-up period, he was still putting out between 2000 and 3000 mgms. per cent of albumin in the urine with but an occasional red blood cell. Symptomatically, his course has been characterized by exacerbations and remissions of generalized edema.

A second patient who went on to the chronic nephritis and subsequently came to autopsy had a history of intermittent edema of the face for three weeks prior to admission. Similarly this patient upon admission had very large amounts of albumin ranging between 2000 and 4000 mgm. per cent with a relatively few red blood cells. These findings persisted until death, four months after the onset of the disease, due to an intercurrent pulmonary infection.

The persistence of albuminuria with or without hematuria for a period of one year can usually be regarded as indicative of the presence of subacute or chronic nephritis.

No definite correlation could be established between the apparent severity of the clinical picture upon admission and the ultimate prognosis. Two of the three fatal cases were thought to be only moderately ill upon admission

whereas several patients in this series presented a much more severe clinical picture initially and yet ultimately recovered.

The most common cause of death in acute glomerulonephritis in children is congestive heart failure. The three deaths in this series were the results of or were associated with this complication. However, when it is considered that 72 per cent of the patients evidenced clinical signs of myocardial involvement the mortality rate (3.3 per cent) is relatively low.

Addis counts on the urinary sediments, erythrocyte sedimentation rates and observation of serial urea clearance tests are valuable adjuncts during convalescence in determining the prognosis. Concentration and dilution tests, phenolsulfophthalein excretion tests and intravenous pyelography were employed in a few patients but were discarded as routine procedures because they provided no additional information.

TREATMENT

Treatment consisted of absolute bed rest until the urine was free of albumin and red blood cells. Several cases were discharged before the urinary sediment was completely normal and it was felt that the convalescence would be intelligently followed at home. When patients were permitted premature exercise, exacerbations of albuminuria and hematuria were noted on several occasions.

A relatively high protein, high carbohydrate, low fat, salt-free diet was employed with fluids given as desired. In those cases showing a high non-protein nitrogen, fluids were forced. High vitamin supplements were employed routinely. Blood transfusions were given only when convalescence was well advanced and the initial phase of the attack had subsided. Empirically it was thought advisable to avoid the intravenous route in a disease with acute and generalized vascular involvement such as nephritis. In two instances when blood transfusions were given during the first few days after the onset of the symptoms of nephritis, gross hematuria ensued shortly thereafter.

Sulfadiazine, sulfapyrazine and penicillin were employed when a susceptible infection was concomitantly present, without any untoward reaction being noticed. Penicillin would appear to be the drug of choice for the treatment of such coexisting extra-nephritic infections, since in the presence of impaired renal function, sulfonamides may be retained with the production of an inordinately high sulfonamide blood level. Regarding the use of chemotherapeutic agents for the treatment of nephritis per se, Rapoport et al.[15] in a series of 33 patients with acute glomerulonephritis treated with sulfonamides, found no appreciable difference when compared with a control group of 40 patients who were not treated with this drug. Similarly, penicillin cannot be expected to influence significantly the course of acute glomerulonephritis.

Magnesium sulphate (0.2 cc. per kilogram body weight of a 25 per cent solution) was given intramuscularly in those cases manifesting cerebral symptoms or in those patients who showed a rising blood pressure. The dosage was repeated every two to four hours until hypertension was under control and/or signs of cerebral encephalopathy disappeared. The intramuscular route was found adequate and in no instance was the magnesium sulphate given intravenously. It has been shown that this drug exerts its beneficial effect on hypertensive encephalopathy associated with acute glomerulonephritis due to the relaxation of the arterial spasm rather than to the production of diuresis with diminution of the degree of cerebral edema. The magnesium ion has a relaxing effect on this vaso-spasm[16].

Surgical procedures were not contraindicated by the presence of acute glomerulonephritis when they were deemed advisable but elective operations were deferred. Hypertonic solutions were given to several patients in an attempt to mobilize the edema without success. Mercurial diuretics were not employed on general principles because of the potential harmful effect of these drugs upon an already damaged kidney. Xanthine derivatives did not appreciably hasten diuresis in the several cases in which they were employed. Intake-output records were discarded as a tedious and unreliable procedure in children and equally valuable information was obtained by daily weighing and observation of the resultant weight curve. Only a few of the patients in the early part of this series were digitalized; however, in the later group, the majority received digitalis for the treatment of congestive heart failure. While it is true that most patients with congestive failure due to acute nephritis will respond to bed rest alone for repair of their cardiac function, it is considered advisable to digitalize all patients with decompensation because of its possible serious import. In contrast to the deleterious effect of digitalis not infrequently noted in patients with acute rheumatic myocarditis, no untoward reactions were noted in the group of nephritic heart failure cases who received this drug. The preparation of choice was digifoline and one cat unit per ten pounds of body weight was employed. One-half the total dose was administered on the first day in three divided doses, then one-half of the remainder on the second day in two doses and the rest on the third day. A maintenance dose of one-half cat unit every day followed until evidence of heart failure had disappeared or toxic symptoms intervened.

CONCLUSIONS

1. A review of the salient clinical features of 90 consecutive cases of acute glomerulonephritis observed at the Children's Hospital during a three-year period (1943–45) is presented. The presenting symptoms and clinical manifestations are noted.

2. Of this series, eighty-four cases or 93.4 per cent recovered, while three (3.3 per cent) died during the acute attack. Three cases (3.3 per cent) developed chronic glomerulonephritis. The three deaths associated with or were the direct result of acute nephritic congestive heart failure.

3. Acute glomerulonephritis has been the most common cause of congestive heart failure at Children's Hospital during the three-year period reviewed (1943–45) and was present in 35, or 57 per cent of the 62 cases of acute nephritis who were examined for evidence of this complication.

4. The treatment employed in this series is indicated and consisted largely of absolute bed rest and the management of symptoms as they appeared. The advisability of administering digitalis to all cases of acute nephritis complicated by congestive heart failure is suggested.

REFERENCES

1. Schwarz, H., Cohn, J. L., and Weiner, B.: New York J. Med., **40:** 409, 1940. Seegal, D., Seegal, B. C., and Lyttle, J. D.: J. Am. Med. Ass'n., **105:** 17, 1935.
2. Lyttle, J. D.: Holt's Diseases of Infancy and Childhood, 11th Ed. pp. 824, 1940. D. Appleton and Century Co., Inc.: New York.
3. Seegal, D., and Earle, D. P.: Am. J. Med. Sci., **201:** 528, 1941.
4. Futcher, P. H.: Arch. Int. Med., **65:** 1192, 1940.
5. Aldrich, C. A.: Brennemann's Practice of Pediatrics, Vol. III, Chap. 28, 1945. W. F. Prior Co., Inc.: Hagerstown, Md.
6. Rubin, M. I., and Rapoport, M.: Am. J. Dis. Child., **55:** 244, 1938.
7. Levy, I. Jesse: Am. Heart J., **5:** 277, 1930.
8. Goodhart, J. F.: Guy's Hosp. Rep.: **24:** 153, 1879.
9. Whitehill, M. R., Longcope, W. T., and Williams, R.: Bull. J. Hosp., **64:** 83, 1939.
10. Marcolongo, F.: Arch. Per. Le Sc. Med.: **59:** 975 and 1025, 1935.
11. Master, A. M., Jaffe, H. L., and Dach, S.: Arch. Int. Med., **60:** 1016, 1937.
12. Longcope, W. T., O'Brine, D. P., McGuire, J., Hensen, O. C., and Denny, E. R.: J. Clin. Invest., **5:** 7, 1927.
13. Brody, H., and Smith, L. W.: Am. J. Path., **12:** 373, 1936.
14. Ash, R., Rubin, M. I., and Rapoport, M.: J. Dis. Child., **65:** 106, 1944.
15. Rapoport, M., Rubin, M. I., and Waltz, A. D.: Am. J. Med. Sci., **211:** 307, 1946.
16. Rubin, M. I., and Rapoport, M.: Am. J. Med. Sc., **201:** 734, 1941.

DEADLINE

May 1st, 1947 is the deadline for entering the $34,000 prize art contest on the special subject of "Courage and Devotion Beyond the Call of Duty" (on the part of physicians in war and in peace). This contest is open to all M.D.'s in the Western Hemisphere. The exhibition will take place in conjunction with the A.M.A. Centennial Session at Atlantic City, June 9–13th, 1947. For complete information, write or wire now to Francis H. Redewill, M.D., Secretary, American Physicians Art Association, Flood Building, San Francisco, California, or to the sponsor, Mead Johnson & Company, Evansville 21, Ind., U. S. A.

ERYTHROBLASTOSIS DUE TO A-O INCOMPATIBILITY

Case Report No. 88

Charles Stiegler, M.D. J. P. 46–10526

The patient, a colored female, was born after 8½ months gestation by a normal delivery at a local hospital on November 14, 1946. There were no apparent abnormalities at birth or during the first day of life. The birth weight was 5 pounds, 8 ounces. Jaundice of increasing severity was noted first on November 15th; the hemoglobin at this time was 78 per cent. An Rh typing on the mother and baby were both positive. As the hemoglobin dropped to 69 per cent later in the day on November 15th, the patient was transferred to Children's Hospital.

On admission to this hospital, physical examination revealed a markedly jaundiced newborn female infant not appearing acutely ill. The liver was palpable 1 cm. below the costal margin, and the spleen was palpable 2.5 cm. below the costal margin. There were no other physical findings of note. A hemogram at this time showed 10.5 gms. of hemoglobin, 2.9 million erythrocytes, 5,200 leucocytes of which 74 per cent were neutrophiles and 26 per cent lymphocytes; a moderate number of erythroblasts were present. The Rh typing was repeated and confirmed. The baby was Type A (Int.) and the mother was Type O (Int.). Studies on the mother's serum yielded no abnormal agglutinins; the anti-A titre ("a" agglutinins) was 1:2048; the anti B titre ("b" agglutinins) was 1:512. The interpretation of this study was as follows: "The titre of "a" agglutinins is well above that usually found in Type O individuals and may explain the hemolytic anemia present in the infant". There was no history of the mother having received blood transfusions at any time. An older sibling, the mother's only previous pregnancy, was Type B (Int.). A Wasserman taken as part of her prenatal care was negative.

The patient was given 60 cc. Type O Rh negative blood on November 15. On November 16 the hemoglobin had risen to 13.5 grams, and the erythrocyte count to 3.95 million. The condition of the patient showed continued improvement following a second transfusion of 50 cc. Type O Rh negative blood on November 19 with no clinical evidence of jaundice on November 21. The hemoglobin was 14 grams and erythrocyte count 4.25 million on November 20, and the patient was discharged November 23.

The patient has been well on follow-up visits to the dispensary. Follow-up studies on the mother's serum on January 8, 1947 revealed an anti-A titre of 1:2048, and an anti-B titre of 1:248.

DISCUSSION

John Cassidy, M.D.: This infant, it is evident, had congenital hemolytic disease of the new born, severe enough to require several blood transfusions. Of interest is the fact that the anemia is not explainable on the basis of iso immunization by the Rh factor but can probably be explained by sensitization to the "a" agglutinogen. It is rather unusual in that this infant was the result of the mother's second pregnancy; the first child belonged to group B. Both mother and infant were Rh positive, the mother belonging to group O (International). Hence normally there are present in the mother's serum "a" and "b" agglutinins. Red blood cells from the infant, containing "a" agglutinogen, escaping into the mother's circulation, stimulate the production of "a" agglutinins. This was evidently the course of events here because the titre of "a" agglutinins in the mother's serum was 1:2048, while the titre of the "b" agglutinins was only 1:512.

From various reports it is estimated that approximately 10 per cent of the cases of hemolytic disease of the new born occur in infants whose mother's are Rh positive. Wiener (1) in a report of 42 such cases found that the blood groups of 34 of the infants proved to be incompatible with those of the mother's, and concluded that A-B incompatibility played an important role in the pathogenesis of the majority of these cases.

The disease in this group is characterized by mildness of symptoms and usually spontaneous recovery. Apparently natural anti-A and anti-B agglutinins are not harmful to the blood of the fetus because of their low titre and because there is apparently a low sensitivity of the "a" and "b" agglutinogens in the fetal red blood cells. Also it is known that "a" and "b" agglutinogens are still imperfectly developed in the human fetus at birth.

It appears that mild or sub-clinical cases of hemolytic disease of the new born due to "a-b" incompatibility are quite common but frequently overlooked. Halbrecht (2) in analyzing and reviewing 10,000 new born infants found 60 cases of a type of jaundice similar to that seen in hemolytic disease of the new born (Erythroblastosis) but in some respects resembling "physiological" jaundice. He designates these cases as "icterus neonatorum precox". Jaundice appeared shortly after birth, the liver and spleen were not enlarged, and occasionally a mild anemia appeared. Of this series, the blood group of the infant was incompatible with that of the mother in 95 per cent of the cases.

Wiener (1) brings out in his report the relatively high frequency with which first born infants are affected, in contrast with those due to iso immunization by the Rh factor. He gives several factors to explain this difference. "Firstly, the Rh factor is restricted to red cells in human

beings, and related antigens are to be found only in the red cells of apes and higher monkeys. On the other hand the "a" and "b" group substances are present in soluble form in the secretions and body fluids of most human individuals and are also ubiquitous in the animal kingdom. Thus, human beings could be sensitized by injection of pooled human plasma, therapeutic horse serum, toxins and vaccines prepared in culture media containing commercial peptone and hog peptone, etc. Finally, human beings have a background of natural "a-b" sensitivity which is lacking in the case of the Rh factor. Accordingly, relatively minute amounts of fetal products containing "a" and "b" factors passing into the maternal circulation early in pregnancy might be sufficient to sensitize her in time to affect the infant, while this could hardly occur in the case of the Rh factor".

The case presented was transfused with type O Rh negative blood. From what has been said it can be seen that the rationale of using type O blood has sound basis since the red cells contain neither "a" or "b" agglutinogen and hence will not be affected by the agglutinins corresponding to these which are present in the serum of the infant.

REFERENCES

(1) Weiner, A. S., Sonn, E. B., and Hurst, J. G.: Pathogensis of Erythroblastosis Fetalis. 111 Illustrative Case Histories of A-B Sensitization. Amer. Jour. Dis. Child., **71:** 1946.

(2) Halbrecht, D.: Role of Hemagglutinins Anti-A Anti-B Pathogenesis of Jaundice of the New Born. Icterus Neonatorum Precox. Amer. Jour. Dis. of Child., **69:** 248, Oct. 1944.

SUB-AORTIC STENOSIS

Case Report No. 89

Clifford J. Tichenor, M.D. C. J. 45-3192

A twenty-three month old white male was admitted to the hospital because of a precordial murmur detected in the "out patient" department during a routine physical check-up.

The infant had been born prematurely at a local hospital on February 23, 1945, the birth weight being 2500 grams. The mother was an indigent but apparently a healthy multipara who had experienced no illnesses during this pregnancy. The delivery was uncomplicated and low forceps were employed. At birth there were no neonatal or post natal difficulties and the infant was said to be active, pink in color and to have well aerated lungs. The physical examination at birth had revealed a precordial murmur which was not thought to be of organic origin.

No feeding problems were encountered in infancy and the vitamin intake was considered adequate. With the exception of being slightly undersized, the infant experienced normal growth, and development. There had been no previous illnesses or operations. Cough, cyanosis, dyspnea and syncope were also denied.

Physical examination at the time of admission revealed an apprehensive, irritable, slightly pale, white male infant, appearing skeletally small for the age of twenty-three months, but presenting no remarkable physical or constitutional symptoms on observation. The weight was 20 pounds, the height 30 inches and the pulse 140. The temperature and respirations were normal. The only remarkable finding was a moderately low, harsh, blowing systolic murmur heard over the right second and third interspaces, being loudest in the second right intercostal space. The heart was enlarged to the right and left by percussion and the point of maximum intensity was at the fifth left space just outside the nipple line. The second heart sound was good and there was no palpable thrill. Finger clubbing and cyanosis were not present and the blood pressure was 96 systolic, and 64 diastolic. The spleen was barely palpable and the liver could be felt 2 cm. below the right costal margin. The remainder of the physical examination was essentially normal. There were no visible pulsating vessels.

Laboratory examination of the blood showed the hemoglobin to be 12.5 grams with 4,280,000 erythrocytes and a normal white cell count. The urinalysis was negative. X-ray examination of the chest revealed the cardiac silhouette to be enlarged to the right and left, and the vascular shadow to be broadened particularly on the right. The appearance was suggestive of a congenital heart lesion.

Two electrocardiograms revealed a sinus tachycardia, the rate to vary between 110 and 140 and the P-R interval to be 0.15. There was a normal axis with upright T-1, diphasic T-2 and inverted T-3. The Q.R.S. complex was 0.06. The interpretation was premature ventricular beats, but otherwise within normal limits.

On the basis of the clinical findings, Dr. B. J. Walsh made a diagnosis of congenital sub-aortic stenosis.

COMMENT

Sub-aortic stenosis is one of the rarer congenital cardiac anomalies. According to Maude Abbott it has sometimes been wrongly diagnosed as acquired aortic stenosis. Sub-aortic stenosis (12 cases of Abbotts' series) involving the infundibulum (out-flow tract) of the left ventricle is more often found as a congenital defect than stenosis of the valve itself, although both are rare. The second heart sound in acquired stenosis is not distinctly heard.

If a patient with a cardiac malformation reaches puberty, there is great probability that some day fever will develop and the symptoms of subacute bacterial endocarditis will gradually become manifest. In general thrombotic deposits are located at points where the blood is driven through a narrow opening or where the blood is propelled against the opposite wall. These observations at necropsy only serve to demonstrate the importance of mechanical factors in the development of bacterial endocarditis. Congenital sub-aortic stenosis, truly rare, must be considered as another heart malformation with a propensity to superimposed infection.

ACUTE APPENDICITIS SIMULATING RHEUMATIC FEVER

Case Report No. 90

Robert Sullivan, M.D. P. H. 46–10409

On the 12th of November, 1946, a ten year old white boy was sent to Children's Hospital by Dr. Charles Martin of Manassas, Virginia with the diagnosis of acute appendicitis and chronic valvular heart disease.

He had seemed perfectly well until three days before when he "caught a cold" and seemed "choked up". His mother gave him a liquid medicine and a white tablet. These medicines are kept on hand for the child's "asthmatic" breathing during colds, to be taken as needed. His nose was running and the cold was mild. At 1:00 a.m. on the day of admission he awoke with severe generalized pain in the abdomen. At 7:00 a.m. he vomited yellowish material with no blood. His bowels had been moving daily and moved on this morning at 7:00 a.m. He had had milk of magnesia (one tablespoon) several times in the past few days and received another this morning. He did not seem to have a fever although his temperature was not taken. He vomited again on the way to the hospital and had been nauseated since then. On arriving here he had no abdominal pain but his abdomen was sore when he coughed. He was coughing infrequently, had no joint pains, had not mentioned precordial pain and was not conscious of a rapid rate. There was no recent shortness of breath and his appetite remained good.

Past diseases included measles, mumps, and chickenpox. At four years of age he had an episode of "asthma" and continued to have "croup and asthma" whenever he caught a cold. These episodes were frequent and severe. In 1943 he had rheumatic fever with swollen, hot and painful ankles and knees. This was treated by bed rest at home for three months. He had had sore throats before this but no joint involvement. In 1944 he was said to have had "spinal meningitis" and was taken unconcious to a hospital in Virginia. He ostensibly made an uneventful recovery.

The child's father has "ulcers of the stomach and something wrong with his back". His mother is aging but has no disease. A cousin died of rheumatic fever at nineteen. There are fourteen living, healthy siblings. Two sisters died of pneumonia and pertussis.

He lives on a farm, drinks unpastuerized milk and well water. He has a dog. There had been no ticks seen in the vicinity recently and he has not handled rabbits. Though ten years old, he is in the second grade.

The admission physical examination recorded him as being well developed and nourished, afebrile, healthy and comfortable. There was no

anemia, jaundice or petechiae. The ear drums had a slight reddish tint. The tonsils were enlarged and the pharynx was reddened. Lungs were clear. Although the P.M.I. could not be located, percussion of the heart suggested a normal size. The rate was 110 per minute and the rhythm was regular. There was a grade III mitral, systolic, somewhat harsh murmur with a rub-like quality. This was of intensity enough to radiate 5–10 cm. in all directions and was constant. The blood pressure was 120/90.

The abdomen was flat. There was no pain at the time of the examination. There was involuntary one plus rigidity in all quadrants. Moderate tenderness was present in the subumbilical region and slightly to the right. Deep pressure elicited very little tenderness in any quadrant and rebound tenderness was absent. Peristalsis was present in the right lower quadrant and elsewhere with a frequency of one sound per four seconds. The liver and spleen were not felt.

Examination of the extremities revealed them to be normal with no joint changes, nodules or lymphadenopathy.

The blood examination on admission revealed 3.65 million red cells, 13,000 white blood cells with 83 per cent polymorphonuclears, five per cent band forms, one per cent young forms and eleven per cent lymphocytes. The specific gravity of the urine was 1.030. There were ten milligrams of albumin and a few white and red blood cells in the sediment.

Because of the possibility of this illness being a flare-up of rheumatic fever, a period of observation and a trial of aspirin therapy was decided upon. Forty-five grains of aspirin by retention enema were administered but could not be retained. An intravenous infusion of 400 cc. of five per cent glucose in normal saline was given and in forty minutes the boy had a short chill with a temperature of 104.4°. He slept through the night without complaint. The next day the temperature was normal in the morning and rose to 104.0° in the afternoon. There were transient abdominal complaints but the physical findings were unchanged as were the blood examinations and urinalyses. An X-ray of the chest suggested only a primary complex. An electrocardiogram was negative. The sedimentation rate was 44 mm. per hour. Because bacterial endocarditis was strongly suspected, three blood cultures were taken on successive days, but all were negative. In spite of the septic temperature he still did not seem very ill and his appetite remained good. He had spontaneous bowel movements. The urine remained concentrated to 1.030 and always contained a few white blood cells.

On the fourth day the picture changed. The temperature remained normal and the variable abdominal findings seemed to lessen so that there was only a mild degree of generalized rigidity with slight residual tenderness

in the left lower quadrant. During the early morning hours of the fifth day, the child began having increasingly severe generalized abdominal pain. He felt chilly and at 8:00 a.m. his temperature was 104°. He passed four liquid stools, was nauseated but did not vomit. There was an aching in the right shoulder region and suprapubic pain on urination. Examination revealed him to be much sicker in appearance and he preferred to lie on his left side. The abdomen was slightly distended and tenderness and hyperesthesia were marked everywhere. An upright flat plate failed to reveal anything of significance. Peristalsis was absent and a rectal examination revealed moderate generalized tenderness. Following this, the course was that of a generalized peritonitis with a large abscess localizing in the left lower quadrant by the ninth day. Dr. McNamara incised this and obtained thin yellow pus with a fecal odor from which E. coli and a non-hemolytic streptococcus were cultured.

DISCUSSION

Dr. McNamara: I saw the child three days after admission when he had a soft abdomen with some tenderness in the lower half. There was no muscle rigidity but the right rectus was more tender than the left. Dr. Detweiler and I both agreed that if rheumatic fever could be ruled out we would operate without delay. I saw the child again the next day. The temperature was down to 99° and the abdominal findings were much improved. There was stil some tenderness but decided improvement. Continuation of careful observation was considered advisable. An E.K.G. was done and found to be negative. I saw the child again Saturday at 1:00 p.m. He had had a retention enema of sodium salicylate that morning. He was really sick now with a tense abdomen, more marked on the left side. The findings were quite consistent with acute generalized peritonitis, with abscess formation in the left lower quadrant extending to the umbilical line. The patient was taken to the operating room and a left McBurney incision was made. Foul-smelling, thin yellow pus gushed out of the peritoneal cavity. No further exploration was attempted. Post operative therapy consisted of streptomycin, penicillin, intravenous crystalloid fluids and blood. The progress has been quite satisfactory since then.

Dr. Walsh: I saw the child on the fourth day. He was not particularly sick then. He had evident rheumatic heart disease with mitral regurgitation. The abdomen was as Dr. McNamara described. I thought of two things: (1) Bacterial endocarditis and (2) Rheumatic fever. Rheumatic fever is a very common cause of abdominal pain in children. In twenty per cent of children with rheumatic fever, abdominal pain is their first complaint. The abdominal pain is significant and in thirty per cent they

had abdominal pain at some time in their illness. There is nothing specific about the pain. It may be very slight or very severe simulating generalized peritonitis with rigidity.

There was no evidence at this time to sway one to an intra-abdominal condition. I saw the child again late Saturday afternoon. The patient was now very sick. He was lying on his left side with the knees flexed. Definite signs of generalized peritonitis were present. We could not exclude rheumatic fever yet. On the 15th the temperature was normal for twenty-four hours after doubling the salicylates. This was in favor of rheumatic fever.

On Sunday we discussed the case again and decided to give one more trial of salicylates. This was given intravenously since the child could not retain it orally. Sixty grains in 200 cc. saline were to be given at a rate of 20 to 25 drops per minute. No perceptible response was observed. This was considered a good point against rheumatic fever.

We actually have not learned anything from this case. Anyone who overlooks rheumatic fever as a cause of abdominal pain will soon learn his folly. One should operate with good evidence of a surgical abdomen even in the presence of a positive rheumatic history. As for the anesthesia, a few remarks are pertinent.

1. A skilled anesthetist is essential if inhalation anesthesia is to be done.
2. Nitrous oxide and cyclopropane definitely should *not* be used.
3. Carry the patient as lightly as possible.
4. Spinal anesthesia is the safest.

FOLLOW-UP NOTE

After forty-one days of hospitalization he was discharged in good condition. Three weeks later he was seen as an out patient and was asymptomatic and had gained seven pounds. At Dr. McNamara's suggestion he will return to the hospital in April for an interval appendectomy.